Association of Shock, Coagulopathy, and Initial Vital Signs With Massive Transfusion in Combat Casualties

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Background: Timely initiation of a massive transfusion (MT) protocol is associated with improved survival and reduced transfusion for patients requiring MT; however, a priori identification of this population is difficult. The objective of this study was to compare the results of an MT prediction model and actual MT incidence in combat casualties.

Methods: We performed a retrospective review of the Joint Theater Trauma Registry transfusion database for all US service personnel injured in combat during overseas contingency operations who received at least 1 unit of blood. Systolic blood pressure at the time of admission, heart rate, hemoglobin, international normalized ratio, and base deficit were used in a previously developed prediction model for MT.

Results: Casualties (n = 1124) were identified who had received at least 1 unit of blood and had all data points. Of these patients, 420 patients (37%) received an MT. Subjects presenting with any two of four possible variables (heart rate >110, systolic blood pressure <110 mm Hg, base deficit ≤−6, and hemoglobin <11) had a 54% incidence of MT with a model sensitivity of 69%. Patients predicted but not observed to receive an MT had earlier time of death and an increased incidence of head injuries compared with those predicted and observed to receive an MT. Patients not predicted but observed to receive an MT had increased chest, abdominal, and extremity injuries than those neither predicted nor observed to receive an MT.

Conclusion: The decision to implement an MT seems to rely heavily on clinical evaluation of severity of abdominal and extremity injury rather than physiologic derangement. Using a model based on the physiologic parameters—a more objective measure—may decrease mortality in combat casualties.

Key Words: Massive transfusion, Plasma, Trauma, Hemorrhage, Shock, Coagulopathy.

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Of the causes of potentially preventable death after trauma in military casualties, the majority die from hemorrhage.[1,2] Hemorrhage presents a significant challenge to the clinicians in the setting of traumatic injury in that a balance must be achieved between adequate end-organ perfusion without promoting fluid overload or thrombus disruption. Going too far in either direction on the scale of resuscitation can adversely affect mortality. Further, tissue damage or destruction and resultant hypoperfusion results in early coagulopathy in trauma patients and seems to increase linearly with Injury Severity Score (ISS) and risk of death.[3,4] The term acute coagulopathy of trauma shock has been suggested by Hess et al.[5] to describe this phenomenon.

Following the principles of damage control resuscitation (DCR) allows us to strike a balance between adequate end-organ perfusion while minimizing disruption of the body's own protective clotting mechanisms.[6,7] The recognition and control of surgical bleeding remain the *sine qua non* for survival. However, before reaching the operating room or in transit, DCR advocates for permissive hypotension, attempting to minimize exacerbation of hemodilution while allowing stabilization of the clot.[8] DCR focuses on treatment of acute coagulopathy of trauma shock, which involves the replacement of what the patient has "bled out." This entails transfusing red blood cells, fresh frozen plasma (FFP), and platelets in a 1:1:1 ratio.

In line with the concept of DCR, massive transfusion (MT) protocols have been adopted at several well-organized level I trauma institutions in an attempt to replace "shed" blood, providing early and sustained transfusion of blood products to critically injured patients.[9] However, these protocols are highly variable and are often used to treat dilutional coagulopathy. Data are now emerging, which show that earlier use of plasma and a higher ratio of plasma to packed red blood cells (PRBCs) (<1:2) during MT improve survival and reduce transfusion needs.[10–20] Moreover, predefined MT protocols that deliver higher ratios of FFP have also been shown to reduce mortality[10,11] and overall blood products transfused,[10,21] although their benefit may not extend to those receiving a lesser amount of blood products.[11]

Of all civilian trauma patients, 20% are transfused a unit of blood early after admission; but only 2% to 3% go on to receive an MT.[22,23] The use of MT increases to more than 10% for military casualties and reflects a different wounding mechanism and increased injury severity in this population.[22–25] MT patients typically consume more than 60% of blood products administered and represent a significant pro-

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portion of inhospital morbidity and mortality.[22,23,26] Therefore, the ability to accurately predict which patients will or will not require an MT is especially important in theater, where quantity of blood products available is limited. Timely and efficient activation of an MT protocol allow increased plasma and PRBCs to be started early in those who will benefit and avoided in those who will not.

To determine the driving forces behind a clinician's decision to implement an MT, we used a previously published, slightly modified model based on initial vital signs (systolic blood pressure [SBP] and heart rate [HR]) and laboratory values (base deficit [BD] and hemoglobin [Hgb]) to predict the need for MT in combat casualties and compared the predicted outcomes with real outcomes.[23] We scrutinized the time of death and Abbreviated Injury Scale (AIS) to investigate differences between predicted and observed incidence of MT.

METHODS

We performed an institutional review board-approved retrospective review of all US military personnel who were wounded during overseas contingency operations (OCOs) and received at least 1 unit of blood (n = 2104). These data, collected between March 2003 and June 2008, were obtained from the Joint Theater Trauma Registry, which is currently maintained at the United States Army Institute of Surgical Research. The Joint Theater Trauma Registry transfusion database is a US Department of Defense database established to prospectively collect data from multiple clinical and administrative systems.

Demographic, laboratory, and physiologic data were collected as well as blood products transfused and subject outcome. Four data points were included in our analysis of the patient's likelihood of needing an MT. When missing data points were encountered, the subject was not included in the analysis. After these exclusions, the patient population totaled 1,124.

Blood transfusions consisted of PRBCs and fresh whole blood or a combination of both. An MT was defined as ≥10 U PRBC/24 hours; and for ease of use, 1 unit of fresh whole blood was predefined as equivalent to 1 U PRBC. Based on a review of the literature, variables found to be predict an MT were HR >105, SPB <110 mm Hg, Hgb ≤11, BD ≤−6.[23,25,27,28] We used a cutoff point of HR >110 for ease of remembrance and use. In an attempt to further increase ease of use for a treating physician, we transformed McLaughlin's equation into a "clinical formula." We applied the mathematical and clinical formula to all patients and determined that the presence of at least two variables produces the most optimally sensitive and specific test. Laboratory values included in analysis were drawn at patient arrival and were readily available early after admission, and physiologic variables were the first recorded vital signs. In addition, the mortality rates, time to death in minutes, and AIS among several cohorts were compared. All populations compared were nonparametric, and statistical analysis was performed using the Mann-Whitney *U* test for continuous variables. Categorical variables were examined using a χ^2 analysis. Significance was determined to be $p \leq 0.05$ for all comparisons.

RESULTS

There were 1124 patients with a full set of data points included in our analysis with a mortality of 15%. There were 420 patients (37%) with an MT and 704 (63%) patients without an MT. Mortality was increased for patients with MT compared with without MT, 20% versus 13%, respectively ($p < 0.05$). The majority of PRBCs (75%) administered in the first 24 hours of admission to the combat wounded went to those patients receiving an MT.

Demographic and clinical characteristics by MT status are listed in Table 1. Every variable analyzed was statistically significant with the exception of temperature and age. Patients who received an MT had a higher median HR and lower median SBP than patients who did not receive an MT. Moreover, patients receiving an MT had more severe metabolic derangements as evidenced by a greater BD and lower Hgb. The ISS of the MT patients was expectedly higher than that of the non-MT patients.

Looking at the four chosen data points of our model, we separated patients into groups based on the number of variables present (i.e., 0, ≥1, ≥2, ≥3, or 4 variables present). We then looked at the rate of MT observed in each of these patient groups (Fig. 1). An examination of the population

TABLE 1. Demographic Characteristics of the MT and No MT Cohorts

Variable	No MT	MT	*p*
Age (yr)	24 (21 to 29)	24 (21 to 28)	0.967
SBP (mm Hg)	121 (103 to 138.5)	108 (82 to 129.5)	<0.0001
HR	98 (80 to 119)	117 (94 to 135.5)	<0.0001
Temperature (°C)	98 (97.3 to 99.1)	98 (97 to 99.15)	0.434
Hgb	12.5 (10.9 to 13.9)	11.4 (9.6 to 13.1)	<0.0001
BD	−3 (−6 to −1)	−7 (−120 to −3)	<0.0001
INR	1.25 (1.1 to 1.5)	1.4 (1.2 to 1.8)	<0.0001
PRBCs	4 (2 to 6)	16 (12 to 24)	<0.0001
ISS	17 (10 to 26)	22 (16 to 29)	<0.0001

Data are presented as median (Q1 to Q3).

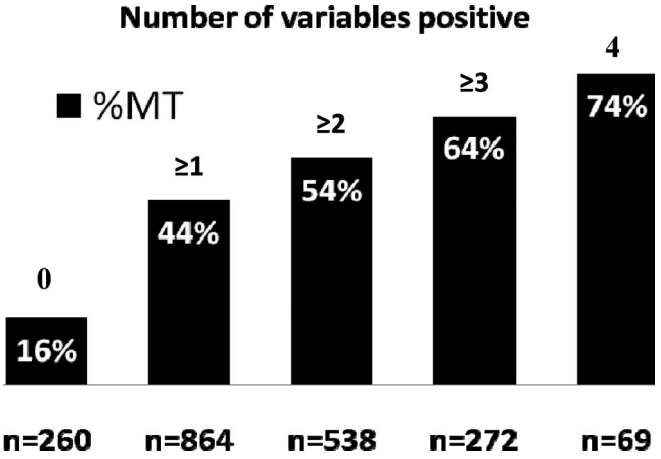

Figure 1. Mortality rates associated with multiple variables present in our clinical model.

from a clinical perspective showed that only 69 (6%) patients possessed all four characteristics; however, 74% (53 of 69 patients) of those patients received an MT. Two hundred seventy-two of 1124 patients had three or more variables present with an MT rate of 64%. Five hundred thirty-eight of 1124 patients had two or more variables positive with an MT of 54%. Eight hundred sixty-four patients had at least one variable positive, leaving only 260 patients of the entire examined population without any of the variables positive. However, this patient population still had an MT rate of 16%. When the presence of any two clinical variables is included as a marker for MT needs, sensitivity is 69% with specificity of 65% (positive predictive value 54% and negative predictive value 78%).

We then cross-referenced those patients who we predicted to need an MT with those observed to receive an MT. These groups were denoted in the following manner: not predicted and not observed to receive an MT (NP/NoMT), not predicted but observed to receive an MT (NP/MT), predicted but not observed to receive an MT (P/NoMT), and predicted and observed to receive an MT (P/MT). We also examined the percentage of patients in each group who presented in shock, which we defined as BD ≤ -6. In patients not predicted to receive an MT, the incidence of shock was low whether they received an MT (11.5%) or not (10%). In addition, the incidence of shock on admission was increased in the predicted compared with the NP group, 78% versus 63%, respectively ($p < 0.05$).

For patients not predicted to receive MT, those observed with MT had increased mortality but similar time to death compared with patients not observed to get MT (Table 2). For patients predicted to require MT, mortality was similar; whereas the time to death was decreased for patients predicted but not observed to receive an MT (Table 2). For patients observed to receive MT, mortality was increased and time to death was decreased for patients not predicted to receive an MT (Table 2). Patients not observed to receive MT also had increased mortality and decreased time to death compared with patients not predicted to receive an MT (Table 2).

The demographics and physiologic variables of each cohort and their comparisons are seen in Table 3. Overall, the demographics of patients in the NP/NoMT group were not statistically different from the NP/MT group; the same is true for the patients in the P/MT and P/NoMT groups. Based on this distinction, these four original groups have been combined according to the MT prediction status (Table 3). Statistical differences for the medians of SBP, Hgb, and BD were measured between these two larger combined groups (Table 3, values in bold denote statistical significance) as expected because of our selection criteria.

Finally, we examined the distribution of AIS for each of the aforementioned cohorts to explore why the provider

TABLE 2. Mortality Rates (%) after Cross-Referencing Four Cohorts: Predicted vs. Observed Massive Transfusion

	Observed		*p* χ^2 Test/Mann-Whitney *U* Test
	No MT	**MT**	
No predicted MT	6%	14%	0.002/0.36
	1,265 (137–15,840)*	1,711 (368–21,600)*	
	n = 455	n = 131	
Predicted MT	**25%**	23%	0.63/0.004
	107 (36–1,617)*	297 (111–4,320)*	
	n = 249	n = 289	
p			
χ^2 test/Mann-Whitney *U* test	<0.0001/0.001	0.04/0.005	

* Median time of death in minutes (interquartile range).

TABLE 3. Compared Demographics Among Four Cohorts With Median and Significance Testing

	Not Statistically Different When Compared with Each Other		Not Statistically Different When Compared With Each Other		
Variable	**Not Predicted, Not Observed Median (Q1 to Q3)**	**Not Predicted, Observed Median (Q1 to Q3)**	**Predicted, Not Observed Median (Q1 to Q3)**	**Predicted, Observed Median (Q1 to Q3)**	***p***
Age (yr)	24 (21.5 to 31)	25 (22.5 to 32.8)	24 (21 to 30)	23 (21 to 27)	0.312
Temperature (°F)	98.9 (97.3 to 99.8)	98.2 (97.6 to 99.7)	97.7 (96.7 to 98.9)	97.9 (96.2 to 97.9)	0.116
SBP (mm Hg)	134 (110 to 145)	126 (115 to 140)	80 (45 to 108)	80 (60 to 121)	**<0.01**
HR	78 (61 to 104)	95 (80 to 120)	105 (52 to 130)	120 (70 to 140)	0.333
Hgb (g/dL)	12.7 (11.5 to 14)	12.9 (11.7 to 14)	10.3 (9 to 12.2)	9.6 (8.2 to 11.5)	**<0.01**
BD	−5 (−6 to −1)	−5 (−7.5 to −2)	−11 (−20 to −8)	−14 (−18 to −9)	**<0.01**
INR	1.66 (1.22 to 2.25)	1.66 (1.0 to 2.0)	1.9 (1.5 to 2.5)	2.1 (1.6 to 2.9)	0.407

TABLE 4. Difference in Subsets of the Two Overall Groups (Predicted or Not Predicted) to Receive a Massive Transfusion

Injury Severity Score ≥3	NP/No MT (n = 455)	NP/MT (n = 131)	*p*
Head	26%	28%	0.72
Face	7%	9%	0.316
Chest	22%	24%	0.629
Abdominal	15%	29%	**<0.001**
Extremities	56%	67%	**0.03**
External	4%	4%	0.87
Injury Severity Score ≥3	**P/NoMT (n = 249)**	**P/MT (n = 289)**	***p***
Head	29%	21%	**0.02**
Face	6%	5%	0.55
Chest	24%	36%	**0.002**
Abdominal	12%	27%	**<0.001**
Extremities	56%	78%	**<0.001**
External	11%	7%	0.08

Boldface denotes statistical significance.

decision to transfuse may have been different from our model's prediction (Table 4, boldface denotes statistical significance). Of patients predicted to need an MT, the P/NoMT patients had more head injuries than the P/MT patients (29% vs. 21%). In contrast, the patients in the P/MT group had more severe chest (36% vs. 24%), abdominal (72% vs. 28%), and extremity (78% vs. 56%) injuries than the P/NoMT patients. Of all patients who were not predicted to need an MT, patients in the NP/MT group had more severe abdominal (29% vs. 15%) and extremity injuries (67% vs. 56%) than the NP/NoMT group.

DISCUSSION

Promptly recognizing when a critically injured patient needs an MT is paramount. We have applied a model based on the physiologic parameters to a large population of combat casualties and compared the predicted outcomes with incidence of MT. When compared with actual outcomes, we are still missing up to 25% of potentially preventable death when an MT was not administered. From further examination of four subpopulations (predicted vs. observed MT), we believe that the decision to implement an MT is subjective and based primarily on abdominal and extremity injuries rather than objective data (physiologic variables).

Hemorrhage is the leading cause of death deemed preventable or potentially preventable and accounts for the majority of deaths occurring within 48 hours after hospital admission.[11] In fact, exsanguination is the primary cause of death in the first hour after traumatic injury.[29] Recent studies show that more than 25% of trauma patients present coagulopathic as reflected by abnormal values for prothrombin time (PT) and partial thromboplastic time (PTT).[4,30,31] Although international normalized ratio and BD are good predictors of mortality, by themselves, they cannot discriminate those who will (or will not) go on to receive an MT. However, when a combination of multiple variables is analyzed in a population of combat casualties, the predictive ability of the "clinical formula" is somewhat strengthened. In our clinical model, independent predictors of MT were Hgb <11, BD ≤ -6, HR >110, and SBP <110 mm Hg (sensitivity 69%). With rapid point of care testing and physical examination, these variables are available during initial trauma workup and may assist in the rapid identification of those at risk for MT, allowing resources to be quickly marshaled.

Several models for rapidly predicting which patients will go on to receive an MT are in the literature.[7,23,25,27,32,33] Many use a combination of dichotomous variables that are obtained rapidly in the trauma bay and are readily accessible after the patient's arrival. Three studies are based on combat wounded, consisting of both coalition and noncoalition forces and civilians.[7,23,32] We used a slightly modified version of the model set forth in the study by McLaughlin et al., which predicts MT by variables of HR >105, SBP <110 mm Hg, pH <7.25, and Hct <32. The incidence of MT with area under the receiver operator curve for this model was 0.747 (McLaughlin et al.[23]), comparable with other models at 0.618 (Cancio et al.[32]) and 0.804 (Schreiber et al.[34]). McLaughlin et al.[23] report positive predictive and negative predictive values of 66% and 72%, respectively, and an 11% incidence of MT when no variables were present. The variables in our predictor equation are similar to all the aforementioned studies in that an acute measure of anemia and shock state (i.e., Hgb and BD) remained in the final equation. Mechanism of injury and pH were not recorded in our database. In our analysis, using HR as 110 as the cutpoint did not produce significantly different results compared with 105; therefore, the cutpoint for HR was increased to 110 beats per minute from the study by McLaughlin et al., for ease of use in future emergency department applications. This study used the same patient population as McLaughlin et al.'s group as a part of our overall population; however, the database has since expanded by approximately fourfold since their study, giving us a greater power in our analysis. Using this expanded sample provides a clinical model with positive and negative predictive values of 54% and 78%, respectively, with a 16% incidence of MT when no variables are present.

Other models in the literature use physical abnormalities or tests designed to detect such abnormalities.[25,27] The model set forth by Nunez et al.[25] comes from a civilian population and uses a scoring system based on the presence of penetrating injury, SBP <90 mm Hg, HR >120, and positive focused assessment sonography in trauma (FAST) or abdominal AIS ≥ 3 to decide when to activate an MT protocol. The intent of its design was to make the calculation easy to determine so as not to delay activation of MT; and as such, no laboratory variables were evaluated in this study. When two predictive variables were present, this model correctly predicted 84% of MT and reports area under the receiver operator curve of 0.86; however, the predictive ability between this model and the score of McLaughlin et al. is not different. In this study, the injury mechanism is almost exclusively penetrating, giving little ambiguity as to the presence of ongoing hemorrhage or severe internal tissue

damage as is sometimes the case in blunt abdominal injury. For this reason, the FAST examination is less useful variables for predicting MT in our population. In addition, FAST examination depends on the skill of the user and may lose sensitivity because of body habitus or injury pattern (i.e., pelvic fracture).[35–38]

Although these scoring systems differ in physiologic, laboratory, and anatomic variables, they are all easy to use, allow objective data to be assigned to each patient in the trauma bay, and have the same predictive power for MT. The application of these models may improve the uniformity of use and earlier activation of MT protocols, thus positively affecting mortality and decreasing pressure on blood bank resources.[11,18,21,39] However, these models may still miss up to 25% of patients requiring an MT. This point is highlighted by our time of death data: the median time of death in the P/NoMT group was only 107 minutes compared with the median time of death of 297 minutes in the P/MT patient population, indicating that the former cohort may have died before receiving the benefit of the MT. This notion is further strengthened by the fact that we did not see any demographic statistical difference between the aforementioned two groups (P/NoMT vs. P/MT), suggesting that in fact these two patient populations may have had the same life or death outcome if a predicted MT would have been called for earlier or at all.

In trying to determine why at times our model's predictions differed from the surgeon's decision, we saw the decision not to administer an MT in patients who were predicted to need one in patients with higher percentage of head injuries. The reason that an MT was not thought to be necessary may have been that the level of illness was difficult to pinpoint in that subset of patients as presence and severity of head injury are not always easy to diagnose. The P/MT group had more obvious (abdominal, chest, and extremity) injuries than the P/NoMT group.

Among the patients in NP/MT group, more obvious injuries in the truncal region and extremities were present than patients in the NP/NoMT group, indicating that these types of injuries heighten the concern in the provider and lowers the clinical evaluator threshold for implementing an MT. Our data seem to indicate that although physiologic derangements (i.e., BD ≤ -6) may have existed in a significant number of patients, these alterations were not the main factor behind the administration of an MT. Obvious abdominal injuries seem to be the driving factor behind implementation of MT rather than overt hemodynamic or laboratory abnormalities. Yucel et al. showed that the inclusion of physical factors in a predictive model for MT lends more precision to the model, a point they demonstrated through the development of their Trauma-Associated Severe Hemorrhage Score. The Trauma-Associated Severe Hemorrhage Score incorporates laboratory data, vital signs, and the presence of both long bone and pelvic fractures; surgeon experience level lends accurate diagnosis solely from a physical examination in such situations when imaging is not available.[27]

Several important limitations exist: First, we currently do not have time stamps showing when our blood products are given; therefore, the temporal value of early administration of blood products in our study cannot be determined. Second, our study is also retrospective and is restricted by data that were available and collected during the study period. Third, this study extends for more than 5 years and was collected from combat wounded in two disparate theaters. As the battlefield matured, blood products became more available, and evacuation times were shorter. Moreover, a Clinical Practice Guideline was implemented in March 2006, which recommended that physicians in theater use damage control principles in resuscitating combat wounded. Fourth, although it was strongly predictive of MT and death, ISS was not included in either model because it is usually not known at the time of admission. Finally, this study represents a select group of battlefield casualties with penetrating injuries, both of which may limit comparisons of our study with the general civilian population.[40]

Not knowing timing and type of blood product administered prevents us from making conclusions based on the outcomes related to the optimal formulation of an MT protocol, and any survival bias for patients who received a higher ratio of FFP:PRBC in this population still remains unknown. A higher transfusion ratio of PRBC, plasma, and platelets and less crystalloid were our standard practice after implementation of the Clinical Practice Guideline (Simmons, unpublished data). However, the diversity of care providers and clinical skill sets has broadened since the initial involvement of the US military in OCOs. Although it may play a small role now in MT incidence, it may be more of a factor in the number of MTs in the later years of the conflict.

Although our model is based on the retrospective data, it provides framework for the next step in analysis: a prospective multicenter trial to observe and validate the model. The Prospective, Observational, Multi-center Massive Transfusion study (http://www.uth.tmc.edu/cetir/PROMMTT/) is currently underway and is designed to compare the model's ability to predict the need for MT with the predictive ability of the trauma surgeon's clinical judgment. This study will possibly support our current study findings: that the decision to implement an MT is based mainly on injury severity (anatomic abnormalities) and is quite subjective, relying heavily on surgeon experience. If this finding is proven true, our model could serve to circumvent the bias of provider experience when deciding who should receive an MT.

CONCLUSIONS

Data are now accumulating that MT protocols that call for earlier transfusion of plasma with higher ratios of FFP to PRBC improve overall survival.[9,25] However, most centers with MT protocols do not have standardized initiation policy, and it is often left up to the provider's judgment. Although several predictive models exist, these studies may miss up to 25% of patients within this population, a majority of who will benefit from the activation of such a protocol. Our scoring system, based on data from more than 1,100 combat casualties from OCOs, indicates that a combination of Hgb <11, BD ≤ -6, HR >110, and SBP <110 mm Hg somewhat predicts need for MT; and these variables are usually available within 5 minutes of admission. Our predictive model is

easy to use, and our analysis indicates that it can be used rapidly by the on-call physician to improve confidence in deciding when to call for an MT, regardless of surgeon's experience. In addition, the model may be of benefit in obtunded trauma patients at initial presentation, at which time injury severity may be unclear.

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DISCUSSION

Dr. Kenji Inaba (University of Southern California, Los Angeles, CA): I would like to thank ATACCC and the program committee for the privilege of discussing this paper, and I would like to congratulate the authors for their important work targeted at identifying the predictors of massive transfusion.

In the evolution of damage control resuscitation, one of the practical next steps is to delineate the patient factors that can accurately predict as early as possible those patients that will go on to require a massive transfusion. In this patient population, often defined as those requiring greater than or equal to 10 U RBCs in 24 h, the early aggressive replacement

of plasma in ratios approaching 1:1 has been associated in several retrospective studies with improved survival. Identification of this population will facilitate optimizing resuscitation while decreasing exposure to plasma in those patients who do not need it.

Dr. Larson and her colleagues have examined in their study the impact of shock, coagulopathy, and abnormal vital signs on the need for a massive transfusion. In their series of patients reviewed from the JTTR, they found that although by themselves an elevated INR and base deficit (BD) were poor predictors of massive transfusion, the addition of physiologic measures, including heart rate and systolic blood pressure, improved the predictive ability of their model.

A few questions for the authors:

1. What was the temporal pattern of deaths in each group? The variables studied, particularly coagulopathy and shock, were found to be good predictors of death but not of massive transfusion. Was there any survival bias introduced into the model by not excluding early deaths?
2. Although most research protocols utilize 10 U RBC in 24 hours as the definition of a massive transfusion, much of the aggressive replacement of blood products is front-loaded. Were you able to examine transfusion cut-offs in the first 6 or 12 hours?
3. How did you select the cut-points for your continuous variables? Several predictive models have been published recently, including the TASH score, the McLaughlin and Schreiber studies, and the ABC score. How did the cut-points you selected compare to the values utilized in these prior models?
4. Did you have access to plasma data; and in particular, did the volumes of plasma transfused in the first 24 hours confound the predictive strength of your variables?
5. Did you test for co-linearity between variables such as HR and SBP?
6. Finally, what is the next step? How should we use the results of your study and those of other studies examining predictors to optimize the identification and treatment of patients with the potential of going on to a massive transfusion?

Again, congratulations on your work.

Dr. Claire Larson (U.S. Army Institute of Surgical Research, Fort Sam Houston, TX): I want to first thank Dr. Inaba and all the reviewers for their time in contributing thoughtful and thought-provoking critique of our manuscript. Their comments are in-line with supporting our main goal which is to improve treatment of the critically ill while conserving resources and minimizing harm. We were lucky enough to receive the reviewers' comments early in manuscript revision, and for this reason, the content of our manuscript has significantly changed to address their concerns. Therefore, where applicable, I will attempt to respond appropriately in reference to our latest version.

Since the compilation of our original manuscript, we have included the median time of death of each group, and the results suggest that survival bias should not play a role. The patients in the group predicted to need but who did not receive a MT had a median time of death of 107 minutes which we believe-through clinical experience-is enough time to receive the full MT. Therefore, a timing of treatment is not the main issue, in our opinion, but rather the timing of *initiating* the MT may be the real problem at play here. We believe that many providers are basing their decision to initiate a MT on anatomical rather than physiologic derangements, which may be leading to unrecognized need for MT. Unfortunately, we do not have the timing of plasma or other blood product delivery or the early ratio of FFP or platelets to PRBCs. We do know that clinical practice guidelines have changed in the military between the years of 2006 and 2007, encouraging higher ratios of FFP:PRBC. These changes most likely have had an effect on mortality, however, we are limited by our lack of information with reference to timing of blood product administration.

We have used a previously published, slightly modified model for MT prediction in combat casualties published by McLaughlin and colleagues in 2008; our goal was not creation or a new model or validation of that model, but rather to determine shortcomings in the use of the model. The choice for cut-points for predictive variables is supported by the literature in first study. However, we did change the cut-point for heart rate to improve ease of use in the hectic emergency scenario (as both HR and SBP values will be the same). The weight that HR played in predicting MT in our population did not change whether the cut-point was 110 or 105. Instinctively, HR and SBP are intimately related, however, in our model we found that both variables could be utilized independently as predictive factors and were not statistically co-variable.

Again, the reviewers' time and effort in the development of their critique has been invaluable to us, and we have attempted to incorporate all their concerns in the manuscript. I want to commend them on their further contribution to this body of research which continues to motivate us as trauma providers to improve care for our patients.